

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| | |
|----------------------------|---|
| TITLE (PROVISIONAL) | The potentiality of Algorithms and Artificial Intelligence adoption to improve medication management in Primary Care: a Systematic Review |
| AUTHORS | Damiani, Gianfranco; Altamura, Gerardo; Zedda, Massimo; Nurchis, Mario Cesare; Aulino, Giovanni; Heidar Alizadeh, Aurora; Cazzato, Francesca; Della Morte, Gabriele; Caputo, Matteo; group, D.3.2; Grassi, Simone; Oliva, Antonio |

VERSION 1 – REVIEW

| | |
|------------------------|---|
| REVIEWER | Jacqueline Kueper Western University |
| REVIEW RETURNED | 03-Aug-2022 |

| | |
|-------------------------|---|
| GENERAL COMMENTS | <p>This article conducted a systematic review to summarize published randomized controlled trials that compare AI/algorithms to standard clinical practice for medication management in primary care settings. The quality of studies is assessed and several fields of information extracted: study characteristics, participant characteristics, intervention characteristics, and outcome characteristics. This study helps to close the gap in understanding potential applications of AI in primary care, finding generally positive support for AI to help with medication management.</p> <ul style="list-style-type: none">- Throughout the manuscript both “algorithm” and “AI” are used. AI may include algorithms, but not all algorithms are considered AI – the distinction between the two for the purposes of the study is not clear. Was the purpose to identify tools based on any type of algorithm of which AI is a special type, or is algorithm being used as a synonym for AI?- The abstract mentions two quality assessment tools used. One is for non-RCTs, but being an RCT is part of the eligibility criteria and this tool is not mentioned in the full text – please elaborate on how and why the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies for non-RCTs was used.- Page 3, Figure 1: Records removed before screening included 218 for “other reasons”. What were these other reasons?- Line 30+, Pg 12: Is there a reference for the definition of primary care in the introduction?- Line 46-49, Pg 12: The definition of AI is unclear/contradictory, stating “AI can be considered a new methodology rather than a support tool....ability to adapt to the needs of the patient make this tool...” Clarifying what is meant by AI, including how it was assessed |
|-------------------------|---|

| | |
|--|---|
| | <p>for inclusion criteria (pg 13), would substantially improve the clarity and impact of the work.</p> <p>- Pg 13, Search Strategy: how were the search terms decided upon? Were Subject Heading as well as keyword searches conducted? If the latter, what part(s) of the document were searched (e.g., full-text, title and abstract, metadata)?</p> <p>- Pg 14, line 9-10: where did the standard data-entry electronic form come from? Was it developed especially for this study? Can it be shared as supplemental material for readers who want to know further details about the studies that you identified and included?</p> <p>- Page 17, line 40 – what were the other possible “machine categories” and how were these decided on? The methods state that you extracted “type of AI”, which is what I initially thought this was going to refer to, but CDSS is not a type of AI.</p> <p>- Pg 18, Lines 48-52: Related to the above point, computerized decision support system is a broad term that can be used to describe many types of computer-based interventions (AI, simple non-AI algorithms, dashboards etc.) Further describing some of the other interventions would help to clarify what types of things would not fall under a CDSS category. It would also be useful to describe some of the technical characteristics of the CDSS – were there key characteristics common to all? That differed between them?</p> |
|--|---|

| | |
|------------------------|--|
| REVIEWER | Ildar Fakhradiyev Asfendiyarov Kazakh National Medical University |
| REVIEW RETURNED | 03-Oct-2022 |

| | |
|-------------------------|--|
| GENERAL COMMENTS | <p>1 Title. The title reflects the main subject of the manuscript</p> <p>2 Abstract. The abstract reflects the manuscript. The structure of the abstract is composed perfectly</p> <p>3 Key words. The key words reflects the focus of the manuscript</p> <p>4 Background. The manuscript adequately describes the background, present status and significance of the study.</p> <p>5 Methods. The manuscript precisely describes all methods in adequate detail.</p> <p>6 Results. The research objectives were achieved.</p> <p>7 Discussion. The discussion section is well written.</p> <p>8 Illustrations and tables. All tables are in good quality and appropriately illustrative of the manuscript contents. All photos are of excellent quality</p> <p>9 Biostatistics. The manuscript statistics is well written.</p> <p>10 Units. All units of measurement are given in standart way.</p> <p>11 References. The manuscript contains the latest, relevant sources. No self-citations found, no inappropriate literature sources.</p> <p>12 Quality of manuscript organization and presentation. The manuscript well, concisely and coherently organized and presented. Great style, language and presentation.</p> |
|-------------------------|--|

| | |
|--|---|
| | 13 Research methods and reporting. The authors prepared the manuscript according to the appropriate research methods and reporting. |
|--|---|

| | |
|------------------------|--|
| REVIEWER | Nadia Roumeliotis Department of Critical Care, CHU Sainte-Justine, University de Montréal |
| REVIEW RETURNED | 05-Dec-2022 |

| | |
|-------------------------|---|
| GENERAL COMMENTS | <p>Thank for submitting this systematic review evaluating the effect of AI on drug management in primary care. The subject is interesting and this is a hard topic to address, so I commend the authors on their work.</p> <p>While the review is interesting and relevant, it lacks important details for reproducibility and needs to detail the population, intervention and outcomes in much more clearly and completely. This is critically important in systematic reviews and should follow Cochrane format. Furthermore, the article is quite dense and would benefit from significant English language revision to synthesize sentences and improve clarity.</p> <p>Specific comments:</p> <p>The abstract needs extensive review. While the objective is well stated, the intervention and outcomes are not mentioned clearly (only a long sentence stating it will use PRISMA and PICO format). Please actually state the PICO for abstract. The results are very limited, so the ability to be succinct here is key. Conclusion mentions safety, but the objective of this paper is not safety, so please revise conclusion.</p> <p>Introduction:</p> <p>Define Acronyms: IOM not defined in first sentence.</p> <p>The introduction needs significant editing as it is very lengthy. I like that medication error and adverse drug event are defined but avoid conducting a literature review in introduction and focus perhaps on the current problem (and then in discussion how the paper addressed this problem). Perhaps this means evidence of AI and CDSS success for medication error reduction in multiple hospital settings, but not in primary care. Please watch the use of 'thus' and 'moreover', and they are too frequently used</p> <p>Lines 43-44 and not clear and need to be rewritten. misuse of word 'figures'.</p> <p>Line 61, sentence 'despite it might be argued that...' does not make sense in English and should be rewritten.</p> <p>Methods</p> <p>Clearer presentation of population and setting needed rather than presenting a few search criteria. For example use: the setting in any primary care clinical, or day clinic, for ambulatory setting for patient of all ages (paediatric, adults, elderly)? and the population is general practitioners, or specialists working in primary care (for residents, or nursing or any other...)?</p> <p>The intervention is not well defined. Any intervention of algorithm and changes decision for prescribing? I assume this is electronic, or computerized, but this is not stated. In the search terms there are AI terms but the words 'clinical decision support systems' are not found and I fear that many have led to significant oversight of certain studies. Especially as certain included studies have CDSS as the</p> |
|-------------------------|---|

| | |
|--|--|
| | <p>intervention (which is not exactly AI, and which was not exactly searched for).</p> <p>The outcome of 'drug management' is a little vague'. Later, 'avoided medication errors is stated as the outcome. In addition to medication errors, is harm reduction included? Reduction of polypharmacy (one of the findings) is not a drug error but rather a harm reduction strategy. Please be clear and attempt to reuse the same terms throughout article for this.</p> <p>Perhaps the actual search strategy might be added to supplement for reproducibility.</p> <p>In methods section 2.2 (inclusion) line 60 remove 'screened a pull of 20 articles..[.]' this is results. Just state how review was done. Generally a kappa score of agreement among reviewers is performed. Perhaps state how agreement was evaluated and handled in this review.</p> <p>Results.</p> <p>The fact that an update was conducted should be in the methods. I was confused upon reading results that numbers in text did not correspond to flow diagram described.</p> <p>The numbers from both reviews can be aggregated for the text and just state the total number screened, full text revised and included. The flow diagram should include totals for each box (rather than have reader calculate totals). Also, the flow diagram should detail the reasons for exclusions of certain boxes (incorrection setting n= , intervention n=, outcomes, etc...)</p> <p>The results table is very vague for this type of intervention. Given the heterogeneity of intervention types and setting, the table should detail the intervention (e.g. decision support to reduce drug interaction in patients with more than 6 meds). In addition, the population column 'at-risk' is not clear. At-risk of what? harm, error, toxicity.</p> <p>Please state the setting and population targeted (eg. family physical office for mental health disorders.</p> <p>Please explain why not attempt was made to synthesize results for a meta-analysis (if same outcome).</p> <p>In the text the outcome categories are well described in results section, but these should have been stated as outcomes in methods. And in the results table. "adherence' for example was not included as a stated outcome in methods.</p> <p>All of the above makes reproducibility difficult for this Systematic review.</p> <p>Quality assessment questionnaire can be supplementary material and this is not essential to the manuscript text.</p> <p>The discussion is far too long and dense. It currently is one long 2-page paragraph. Please separate into paragraphs and avoid redefining definitions and classifications. Perhaps focus and what is novel, and what was known already in other settings and future impacts. Please keep strengths and limitations in this section.</p> <p>The manuscript would benefit from revision from a native English speaker and synthesizing of many sentences.</p> |
|--|--|

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This article conducted a systematic review to summarize published randomized controlled trials that compare AI/algorithms to standard clinical practice for medication management in primary care settings. The quality of studies is assessed and several fields of information extracted: study characteristics, participant characteristics, intervention characteristics, and outcome characteristics. This study helps to close the gap in understanding potential applications of AI in primary care, finding generally positive support for AI to help with medication management.

Throughout the manuscript both “algorithm” and “AI” are used. AI may include algorithms, but not all algorithms are considered AI – the distinction between the two for the purposes of the study is not clear. Was the purpose to identify tools based on any type of algorithm of which AI is a special type, or is algorithm being used as a synonym for AI?

Thank you for the precious comment. We totally agree with you about the fact that not all algorithms are considered AI. Our initial primary aim was to focus only on AI-based interventions. Nonetheless, due to the lack of sufficient scientific literature on this specific topic, we decided to expand our investigation also to algorithms adopted in drug management starting from the assumption that AI uses algorithms (but not all algorithms can be considered AI) to support clinical practice. This statement does not imply that algorithms and AI might be considered synonyms but highlights our interest in investigating tools that might ease medical workflow in primary care.

For sake of clarity, we better specified the inclusion criteria in the methods section. Please, see the changes.

The abstract mentions two quality assessment tools used. One is for non-RCTs, but being an RCT is part of the eligibility criteria and this tool is not mentioned in the full text – please elaborate on how and why the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies for non-RCTs was used.

We thank the reviewer for the valuable observation. It was a typo since, as you highlighted, we decided to include only RCTs in the present systematic review, thus it would be inappropriate to use the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies for non-RCTs. We correctly reported the adopted quality assessment scale in the abstract and we ensured that it was coherent throughout the text.

Page 3, Figure 1: Records removed before screening included 218 for “other reasons”. What were these other reasons?

Thank you for the precious observation. We totally revised the PRISMA Flow Diagram and provided the newer and correct version. Figure 1 is now clearer and the reasons of exclusion more detailed.

Line 30+, Pg 12: Is there a reference for the definition of primary care in the introduction?

Thank you for highlighting this missing. We added the relative reference.

Line 46-49, Pg 12: The definition of AI is unclear/contradictory, stating “AI can be considered a new methodology rather than a support tool....ability to adapt to the needs of the patient make this tool...” Clarifying what is meant by AI, including how it was assessed for inclusion criteria (pg 13), would substantially improve the clarity and impact of the work.

We thank the reviewer for the valuable suggestion. Indeed, we totally understand your point and we care about clarifying that in the reported sentence “ability to adapt to the needs of the patient make this tool”, the term “tool” was misused. We replaced it with the term “methodology” as it reinforces the already stated concept “AI can be considered a new methodology rather than a support tool”. Furthermore, we reported the AI definition we based our study on as follows:

“AI, defined by the Encyclopedia of Artificial Intelligence as a field of science and engineering devoted to the computational understanding and reproducibility of intelligent behaviour”.

Finally, we clarified in the “inclusion criteria” section of our paper how AI influenced the screening process as follows:

“In order to be included, articles had to clearly state the application of AI and/or algorithms in the text. A double-check of the intervention methodology was performed to ensure the effective application of AI and/or algorithms, according to the Encyclopedia of Artificial Intelligence definition and the further stated Hintze classification of AI types”.

Pg 13, Search Strategy: how were the search terms decided upon? Were Subject Heading as well as keyword searches conducted? If the latter, what part(s) of the document were searched (e.g., full-text, title and abstract, metadata)?

The keywords, specifically related to our topic, adopted in our search strategy were chosen by reviewing the MeSH terms, available on MEDLINE and consulting the full-texts of current literature.

Pg 14, line 9-10: where did the standard data-entry electronic form come from? Was it developed especially for this study? Can it be shared as supplemental material for readers who want to know further details about the studies that you identified and included?

Thank you for the comment. For sake of clarity, with “standard” we meant an Excel form. The form was developed for this specific study in order to extract all the available data. The data useful to better understand the results were already included in Table 1. However, we can share the empty data-entry electronic form as a supplemental material file.

Page 17, line 40 – what were the other possible “machine categories” and how were these decided on? The methods state that you extracted “type of AI”, which is what I initially thought this was going to refer to, but CDSS is not a type of AI.

We thank the reviewer for the precious observation. We based our choice of considering CDSS as an intervention belonging to the wide field of AI applications on the latest available evidence which identifies CDSS as a machine learning (ML)-based application.

Wyatt J, Spiegelhalter D. *Evaluating medical expert systems: what to test, and how?* In: Talmon JL, Fox J. (eds.) *Knowledge Based Systems in Medicine: Methods, Applications and Evaluation*. Berlin: Springer; 1991:274–290

Karthikeyan A, Garg A, Vinod PK, Priyakumar UD. *Machine Learning Based Clinical Decision Support System for Early COVID-19 Mortality Prediction*. *Front Public Health*. 2021 May 12;9:626697. doi: 10.3389/fpubh.2021.626697. PMID: 34055710; PMCID: PMC8149622.

Kerexeta, Jon & Torres, Jordi & Muro, Naiara & Rebesch, Kristin & Larburu, Nekane. (2020). *Adaptative Clinical Decision Support System using Machine Learning and Authoring Tools*. 95-105. 10.5220/0008952200950105.

Choi, G.H., Yun, J., Choi, J. et al. *Development of machine learning-based clinical decision support system for hepatocellular carcinoma*. *Sci Rep* 10, 14855 (2020). <https://doi.org/10.1038/s41598-020-71796-z>

Then, according to Hintze classification, we established whether they might be included in level I, II, III, and IV.

Pg 18, Lines 48-52: Related to the above point, computerized decision support system is a broad term that can be used to describe many types of computer-based interventions (AI, simple non-AI algorithms, dashboards etc.) Further describing some of the other interventions would help to clarify what types of things would not fall under a CDSS category. It would also be useful to describe some of the technical characteristics of the CDSS – were there key characteristics common to all? That differed between them?

Thank you for pointing this missing data out. As for the definition of clinical decision support system, we intended any system able to support physicians in clinical decision making. Nine out of 14 included articles whose interventions fell within this definition, whereas 4 of them were classified as medication reconciliation methods and one of them as an automated risk assessment tool.

We thank the reviewer for the kindly suggestion about the technical description of the CDSS characteristics. However, in view of the study aims and the research field in which the present review is grounded, we believed that this specification would not be suitable.

Nevertheless, the idea of deepening this specific technical description might become the main subject of further studies related to the same topic. Indeed, we added this specification as a further issue at the end of the discussion section. Please, see the modified paper.

Reviewer: 3

Thank for submitting this systematic review evaluating the effect of AI on drug management in primary care. The subject is interesting and this is a hard topic to address, so I commend the authors on their work.

While the review is interesting and relevant, it lacks important details for reproducibility and needs to detail the population, intervention and outcomes in much more clearly and completely. This is critically important in systematic reviews and should follow Cochrane format.

Furthermore, the article is quite dense and would benefit from significant English language revision to synthesize sentences and improve clarity.

Specific comments

The abstract needs extensive review. While the objective is well stated, the intervention and outcomes are not mentioned clearly (only a long sentence stating it will use PRISMA and PICO format). Please actually state the PICO for abstract. The results are very limited, so the ability to be succinct here is key. Conclusion mentions safety, but the objective of this paper is not safety, so please revise conclusion.

Thank you for the valuable comment. We extensively modify the abstract.

Introduction:

Define Acronyms: IOM not defined in first sentence.

The introduction needs significant editing as it is very lengthy. I like that medication error and adverse drug event are defined but avoid conducting a literature review in introduction and focus perhaps on the current problem (and then in discussion how the paper addressed this problem). Perhaps this means evidence of AI and CDSS success for medication error reduction in multiple hospital settings, but not in primary care. Please watch the use of 'thus' and 'moreover', and they are too frequently used

Lines 43-44 and not clear and need to be rewritten. misuse of word 'figures'.

Line 61, sentence 'despite it might be argued that...' does not make sense in English and should be rewritten.

We thank the reviewer for the valuable observation. We totally revised the introduction.

Methods:

Clearer presentation of population and setting needed rather than presenting a few search criteria. For example use: the setting in any primary care clinical, or day clinic, for ambulatory setting for patient of all ages (paediatric, adults, elderly)? and the population is general practitioners, or specialists working in primary care (for residents, or nursing or any other...)?

The intervention is not well defined. Any intervention of algorithm and changes decision for prescribing? I assume this is electronic, or computerized, but this is not stated. In the search terms there are AI terms but the words 'clinical decision support systems' are not found and I fear that many have led to significant oversight of certain studies. Especially as certain included studies have CDSS as the intervention (which is not exactly AI, and which was not exactly searched for).

The outcome of 'drug management' is a little vague'. Later, 'avoided medication errors is stated as the outcome. In addition to medication errors, is harm reduction included? Reduction of polypharmacy (one of the findings) is not a drug error but rather a harm reduction strategy. Please be clear and attempt to reuse the same terms throughout article for this.

Perhaps the actual search strategy might be added to supplement for reproducibility.

In methods section 2.2 (inclusion) line 60 remove 'screened a pull of 20 articles..[.]' this is results. Just state how review was done.

Generally a kappa score of agreement among reviewers is performed. Perhaps state how agreement was evaluated and handled in this review.

We thank for the suggestion. We edited the text as requested and we have implemented the required parts in the "Methods" section.

Moreover, further information on the methods and analysis applied to the current systematic review can be found in our protocol "Assessing the potentiality of algorithms and artificial intelligence adoption to disrupt patient primary care with a safer and faster medication management: a systematic review protocol" (DOI: 10.1136/bmjopen-2021-057399).

As mentioned in our systematic review, AI programmes and, more generally, intelligent algorithms for primary care settings were analysed. These software include CDSS which, as reported by several Authors (*Investigating the use of data-driven artificial intelligence in computerised decision support systems for health and social care: A systematic review* DOI: 10.1177/1460458219900452; *Computerised decision support systems in order communication for diagnostic, screening or monitoring test ordering: systematic reviews of the effects and cost-effectiveness of systems* DOI: 10.3310/hta14480; *Effects of Computerized Decision Support Systems on Practitioner Performance and Patient Outcomes: Systematic Review* DOI: 10.2196/17283), operate according to different reasoning methods encompassing expert technological systems, machine learning or data-driven AI. Knowledge-based CDSS were the first classes of CDSS that used a data store to draw conclusions without creating new knowledge. To date, non-knowledge-based CDSS are the most common forms used. These AI-supported systems use patient data to analyse relationships between symptoms, treatments and patient outcomes for clinical decision-making. Therefore, we considered it appropriate not to exclude the CDSS results that were obtained from our search string and therefore associated/supported by intelligent algorithms, as evaluating consulting (Shapiro SC. *Artificial intelligence*. In: Shapiro SC. (ed) *Encyclopedia of Artificial Intelligence*, vol. 1, 2nd edn. New York:

Wiley, 1992) and classified according to Hintze classification (A, Hintze MSU. *Understanding the four types of AI, from reactive robots to self-aware beings*. Conversat US. 2016) and reported the inclusion criteria.

Drug management -and all related errors- concern all processes of prescription, dispensing and drug administration. In our study, medication errors per se were evaluated, irrespective of whether they were related to patient harm or not. Furthermore, we analysed the AI application to polypharmacy, which exposes patients to an increased risk of adverse effects. Polypharmacy is considered an error if, among the prescribed medications, some are not necessary (i.e., overprescribing). We edited the text as requested.

We included the full search string in the supplementary materials.

Thank you for the advice. We modified line 60 removing what indicated.

The agreement was handled with tailored group meetings. We specified this issue in Methods section 2.2.

Results:

The fact that an update was conducted should be in the methods. I was confused upon reading results that numbers in text did not correspond to flow diagram described.

The numbers from both reviews can be aggregated for the text and just state the total number screened, full text revised and included.

The flow diagram should include totals for each box (rather than have reader calculate totals). Also, the flow diagram should detail the reasons for exclusions of certain boxes (incorrection setting n= , intervention n=, outcomes, etc...)

We thank the reviewer for the valuable suggestion. We totally revised the PRISMA Flow Diagram and provided the newer and correct version.

The results table is very vague for this type of intervention. Given the heterogeneity of intervention types and setting, the table should detail the intervention (e.g. decision support to reduce drug interaction in patients with more than 6 meds). In addition, the population column 'at-risk' is not clear. At-risk of what? harm, error, toxicity.

Please state the setting and population targeted (eg. family physical office for mental health disorders.

Thank you for the advice. We modified Table 1 accordingly.

Please explain why not attempt was made to synthesize results for a meta-analysis (if same outcome).

We appreciate the comment. As stated in the study protocol, we intended, where possible, to provide a quantitative synthesis of the evidence. However, the great heterogeneity in results reporting we found in the included articles didn't allow a quantitative synthesis of evidence for a meta-analysis (we added it in the text).

In the text the outcome categories are well described in results section, but these should have been stated as outcomes in methods. And in the results table. "adherence" for example was not included as a stated outcome in methods.

We thank for the suggestion. We edited the text as requested.

Quality assessment questionnaire can be supplementary material and this is not essential to the manuscript text.

We appreciate the comment. We reported the quality assessment questionnaire in the Supplementary material.

The discussion is far too long and dense. It currently is one long 2-page paragraph. Please separate into paragraphs and avoid redefining definitions and classifications. Perhaps focus on what is novel, and what was known already in other settings and future impacts. Please keep strengths and limitations in this section.

We thank for the suggestion. We have amended the text as requested by focusing on the main issues and deleting previously reported topics.

The manuscript would benefit from revision from a native English speaker and synthesizing of many sentences.

Thank you for the suggestion. We totally revised the manuscript and synthesized long and redundant sentences.

VERSION 2 – REVIEW

| | |
|-------------------------|--|
| REVIEWER | Jacqueline Kueper Western University |
| REVIEW RETURNED | 03-Feb-2023 |
| GENERAL COMMENTS | <p>The authors have improved the manuscript substantially. Below are some points that would help to further clarify points in the manuscript, including AI vs algorithm vs machine type:</p> <ul style="list-style-type: none">• Abstract: AI acronym should be defined on first use and then used consistently through the abstract. The use of AI and/or algorithms should also be consistently used throughout, e.g., the opening |

| | |
|--|--|
| | <p>sentence says “AI algorithms” which is a different meaning than AI and/or algorithms. How AI is referenced should also be consistently used in the main text.</p> <ul style="list-style-type: none"> • Page 3, Line 30 – Please revise this sentence as AI is not a new approach - people have been working on medical AI for several decades – and the definition in this sentence is narrower than the one in the next. • Page 3, line 47 – up until this point you have only referenced AI so the distinction with algorithms is unclear in the study aim. You could use similar points as in the review responses to make the rationale for broadening to algorithms clearer to readers. • Section 2.3 – thank you for clarifying details about the data entry form in your response to reviewers; however, Table 1 appears to be a quality assessment table rather than the empty data extraction form in Supplementary materials 2? Given that you clearly reference articles in the results (e.g., those that fall under each Hintze classification), providing a data extraction form with all these details is not necessary; however, if you do have the data entry form filled out it would be valuable to include. The empty chart is not necessary. • Section 2.4 – consider including your rationale for using the Hintze classification. |
|--|--|

| | |
|-----------------|--|
| REVIEWER | Nadia Roumeliotis Department of Critical Care, CHU Sainte-Justine, University de Montréal |
| REVIEW RETURNED | 07-Feb-2023 |

| | |
|------------------|--|
| GENERAL COMMENTS | Thank you for addressing the comments. |
|------------------|--|

VERSION 2 – AUTHOR RESPONSE

Abstract: AI acronym should be defined on first use and then used consistently through the abstract. The use of AI and/or algorithms should also be consistently used throughout, e.g., the opening sentence says “AI algorithms” which is a different meaning than AI and/or algorithms. How AI is referenced should also be consistently used in the main text.

Thank you very much for letting us notice this detail. We took care of correcting line 7 as follows: “The aim of this study is to investigate the effect of artificial Intelligence (AI) and/or algorithms on drug management in primary care settings comparing artificial intelligence and/or algorithms with standard clinical practice” and line 27 as follows: “, supporting the hypothesis that AI is an important tool for patient safety.”

Page 3, Line 30 – Please revise this sentence as AI is not a new approach - people have been working on medical AI for several decades – and the definition in this sentence is narrower than the one in the next.

Thank you for stating this important concept. We took care of the misuse of the adjective “new” by rephrasing the sentence at line 30 as follows: “AI is a growingly applied approach that uses learning (mathematical) algorithms”.

Page 3, line 47 – up until this point you have only referenced AI so the distinction with algorithms is unclear in the study aim. You could use similar points as in the review responses to make the rationale for broadening to algorithms clearer to readers.

Thank you for this precious note. As you suggested, we clarified the rationale at line 46, following the review responses we included as follows: “Our initial aim was to focus only on AI-based interventions. Nonetheless, due to the lack of sufficient scientific literature on this specific topic, we decided to expand our investigation to algorithms adopted in drug management as well, starting from the assumption that AI uses algorithms to support clinical practice. This statement does not imply that algorithms and AI might be considered synonyms but highlights our interest in investigating tools that might ease medical workflow in primary care.

Section 2.3 – thank you for clarifying details about the data entry from in your response to reviewers; however, Table 1 appears to be a quality assessment table rather than the empty data extraction form in Supplementary materials 2? Given that you clearly reference articles in the results (e.g., those that fall under each Hintze classification), providing a data extraction form with all these details is not necessary; however, if you do have the data entry form filled out it would be valuable to include. The empty chart is not necessary.

Thank you for this remark. As you noticed, since we did reference articles in the results and due to the already rich content of supplementary materials we would rather not include the data entry form. We did remove the empty chart.

Section 2.4 – consider including your rationale for using the Hintze classification.

Thank you for suggesting this addition. We did specify our rationale in line 40 as follows “After a wide literature search, Hintze classification was chosen based on the following considerations: it offered the most pertinent graduation for our study, it detailed the specifics of the investigated categories, and it was already applied to internationally recognized digital health studies.”